IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Before the Board of Patent Appeals and Interferences

In re the Application of

Inventor	**:**	**Michalakis Averkiou et al.**
Application No.	**:**	**10/576,997**
Filed	**:**	**April 25, 2006**
For	**:**	**SYSTEM AND METHOD FOR ULTRASOUND PERFUSION IMAGING**

APPEAL BRIEF

On Appeal from Group Art Unit 3737
Examiner Parikha Solanki Mehta

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I. REAL PARTY IN INTEREST

The real party in interest is Koninklijke Philips Electronics N.V., Eindhoven, The Netherlands by virtue of an assignment recorded April 25, 2006 at reel 017822, frame 0860.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF CLAIMS

This application was originally filed with Claims 1-19 with Claims 2, 6, and 13-19 canceled in a preliminary amendment. Claims 3, 9, and 10 were canceled in an amendment of July 17, 2009. The remaining Claims 1, 4, 5, 7, 8, 11 and 12 stand finally rejected and are the subject of this appeal.

IV. STATUS OF AMENDMENTS

No amendments or other filings were submitted in response to the final rejection mailed September 23, 2009. A notice of appeal was timely filed on November 30, 2009.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The subject matter of the claimed invention is ultrasonic imaging of contrast agents in vasculature of the body to image blood perfusion in tissue. Ultrasound contrast agents are solutions of tiny microbubbles which are introduced into the blood stream. Since the microbubbles reflect ultrasound echoes much more strongly than blood cells, the agents are useful in imaging blood and blood flow. One application for contrast agents is imaging the blood by receiving echoes from the microbubbles and producing an ultrasound image. The blood containing the microbubbles is highly illuminated in the image by imaging the strong echo signal returned from the microbubbles intermingled with the blood cells.

Another application for contrast agents which is the subject of this invention is imaging perfusion, that is, how well and how fast blood flows into the capillary structure of tissue. The physician waits until blood containing the contrast agent has flowed into the capillaries of the target tissue. The ultrasound probe then sends a strong, unfocused wavefront of ultrasound into the tissue which is referred to as a plane wave, as its wavefront is flat or planar. The strength of the plane wave can be very high (a high MI, or mechanical index) which breaks the microbubbles, or only high enough to disrupt the microbubbles into

smaller bubbles which can dissolve in the blood stream (low MI). The strong plane wave breaks or disrupts the tiny microbubbles so that, at that instant, the capillary structure in the path of the plane wave contains no discernible microbubbles. The strong echoes which return to the probe can be used to form an image of this microbubble destruction. After a short wait, the process is repeated, and microbubbles which have newly arrived in the capillaries are disrupted and return echoes for imaging. The second image or a comparison of the two images provides a measure of where and how fast the blood flow has re-perfused the capillaries with new blood containing the newly arrived microbubbles. The process can be repeated with different waiting times and the re-perfusion of the tissue over different time intervals gauged to measure the effectiveness of the re-perfusion of the capillaries of the tissue. See, for example, US Pat. 5,833,613 (Averkiou et al.)

A problem with this technique is that the plane wave is by definition an unfocused wavefront. This causes poor spatial resolution in the images produced from the echoes. The unfocused wavefront has a transmit lobe pattern with high sidelobes that add clutter to the beamformation process, further degrading the spatial resolution.

The method of the present invention solves this problem of poor spatial resolution, and also allows the re-perfusion process to be

continuously observed as new microbubbles flow into the capillaries. A plane wave is transmitted over a broad first area of the tissue which is sufficient to destroy the microbubbles in the path of the plane wave. The first area is then interrogated with transmit beams which are focused into smaller second areas of the tissue. These transmit beams are insufficient to destroy the microbubbles and produce echoes reflected back from the microbubbles in the smaller second areas. The focused beams thus have low sidelobes which will not produce image clutter. The reflected echoes are focused by the beamformer into receive beams from third areas which are also smaller than the first area and thus have favorable lobe patterns. The echoes of the focused receive beams are used to form an image. The process of transmitting and receiving echoes from the focused beams which are insufficient to destroy the microbubbles can be repeated, providing a series of images which show the buildup of microbubbles as they return to the capillaries in the ongoing supply of new blood flow with microbubbles.

Independent Claims 1 and 11 are supported by the drawings and specification as seen by reference numerals (#) of the drawings and the specification text (pg., ln) as follows:

1. A method of obtaining an ultrasound perfusion image of tissues perfused with blood containing microbubbles, the method comprising:

transmitting a plane wave of microbubble-destroying ultrasound {#32; ¶ [019]} into the tissues, the plane wave of microbubble-destroying ultrasound encompassing a first area of the tissues, the microbubble-destroying ultrasound having an intensity that is sufficient to destroy microbubbles in the tissues that are insonified by the microbubble-destroying ultrasound;

repetitively transmitting a plurality of beams of imaging ultrasound {#36a-n; ¶ [010], ¶ [019]} into the tissues, each beam of imaging ultrasound having a second area that is smaller than the first area, the imaging ultrasound having an intensity that is substantially insufficient to destroy microbubbles in the tissues that are insonified by the imaging ultrasound;

receiving reflections from each of the transmitted imaging ultrasound beams in respective receive beams {#36a-n; ¶ [010], ¶ [019]}, each of the receive beams having a third area that is smaller than the first area; and

processing the received reflections over a sufficient period [#137,#138; ¶ [010], ¶¶ [030]-[031]} to allow re-perfusion of the tissues to provide an ultrasound perfusion image.

11. A method of obtaining an ultrasound perfusion image of tissues perfused with blood containing microbubbles, the method comprising:

using ultrasound to simultaneously destroy substantially all of the microbubbles in the tissues over a first area {#32; ¶ [010]}; and

repetitively using ultrasound {#36a-n; ¶ [010], ¶ [019]} transmitted and received in a plurality of second areas that substantially

encompasses the first area to obtain an indication of the quantity of microbubbles in the tissues that are intact over a re-perfusion time, each of the second areas being smaller than the first area,

wherein the act of using ultrasound to simultaneously destroy substantially all of the microbubbles in the tissues over a first area comprises using a plane-wave beam of ultrasound {#32, ¶ [019]} to simultaneously destroy substantially all of the microbubbles in the tissues over the first area.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether Claims 1, 4, 5, 8, and 11-12 were correctly rejected under 35 U.S.C. §103(a) as being unpatentable over the prior art in view of US Pat. 5,577,505 (Brock-Fisher et al.)

B. Whether Claim 7 was correctly rejected under 35 U.S.C. §103(a) as being unpatentable over the prior art and Brock-Fisher et al. in view of US Pat. 5,706,819 (Hwang et al.)

VII. ARGUMENT

A. Whether Claims 1, 4, 5, 8, and 11-12 were correctly rejected under 35 U.S.C. §103(a) as being unpatentable over the prior art in view of US Pat. 5,577,505 (Brock-Fisher et al.)

Claim 1 describes a method of obtaining an ultrasound perfusion image of tissues perfused with blood containing microbubbles, the method comprising transmitting a plane wave of microbubble-destroying

ultrasound into the tissues, the plane wave of microbubble-destroying ultrasound encompassing a first area of the tissues, the microbubble-destroying ultrasound having an intensity that is sufficient to destroy microbubbles in the tissues that are insonified by the microbubble-destroying ultrasound; repetitively transmitting a plurality of beams of imaging ultrasound into the tissues, each beam of imaging ultrasound having a second area that is smaller than the first area, the imaging ultrasound having an intensity that is substantially insufficient to destroy microbubbles in the tissues that are insonified by the imaging ultrasound; receiving reflections from each of the transmitted imaging ultrasound beams in respective receive beams, each of the receive beams having a third area that is smaller than the first area; and processing the received reflections over a sufficient period to allow re-perfusion of the tissues to provide an ultrasound perfusion image. The inventive method provides improved accuracy in destruction-replenishment perfusion imaging and the calculation of perfusion curves by using a plane wave to uniformly destroy microbubbles in the image field with one or only a few transmissions. With the microbubbles uniformly destroyed, individual beams are used to interrogate the field as it is re-perfused, with the smaller area of the individual beams providing higher resolution needed for accurate imaging and precise perfusion measurements.

Claim 1 was rejected with reference to paragraph [008] of the present specification, which describes how plane waves have been used to image microbubbles in the prior art. In the prior art technique the plane wave is transmitted and echoes returning from the microbubble destruction events are used for imaging. While this would appear at first to be the most efficient approach since only one transmission is needed for imaging, the returning echo signals result from unfocused transmission and have high side lobes, which cause the images to suffer from poor spatial resolution. The method of the present invention seemly takes a less efficient approach, since echoes returning from the plane wave are ignored for imaging and multiple transmit and receive beams focused at small areas within the larger destruction area of the plane wave are needed for image acquisition. However this seemingly more complex and less efficient approach results in highly resolved echoes for imaging. The prior art approach described in paragraph [008] does not use successive, multiple beams focused in smaller areas for imaging.

To provide these missing elements, the Examiner cites Brock-Fisher et al., which are transmitting two successive pulses with different transmit power levels at the same microbubble. Brock-Fisher et al. then differentiate the two returning echo signals from the pulses, with the

difference revealing the harmonic response of the microbubbles. Brock-Fisher et al. are transmitting pulses which are insufficient to break the microbubbles, as the differentiation requires the echoes to return from the same object for the result to provide the desired related echoes. Brock-Fisher et al. are not trying to measure perfusion and give no consideration to microbubble destruction. The Examiner cites col. 2, lines 60-67 of Brock-Fisher et al. to teach second and third smaller areas of imaging ultrasound compared to a first area. However, the cited passage is not directed to the size of areas in the image field, it is directed to aperture size. Specifically, the Examiner refers to the statement to reduce the transmit aperture in order to decrease transmit power. The transmit aperture is the number of elements of the transducer used to transmit or receive ultrasound, and Brock-Fisher et al. decrease the transmit aperture (uses fewer elements) in order to transmit a pulse with decreased transmit power. But a reduction of the transmit aperture will result in a less focused beam, which will insonify a wider area in the image field. The effect is the opposite of that for which the Examiner is contending. In addition, Brock-Fisher et al. are using their apodization to try to separate the harmonic response of the microbubbles from the fundamental transmit frequencies. They are unconcerned with trying to measure re-perfusion. It is therefore respectfully submitted that the prior art

technique and Brock-Fisher et al. are insufficient to render the method of Claim 1 and its dependent claims unpatentable, which calls for destroying microbubbles in a broad area with a plane wave, then successively imaging the return of microbubbles with a succession of imaging transmit and receive beams directed to smaller areas within the broad area to produce highly resolved images of re-perfusion.

Claim 11 describes a method of obtaining an ultrasound perfusion image of tissues perfused with blood containing microbubbles, the method comprising using ultrasound to simultaneously destroy substantially all of the microbubbles in the tissues over a first area; and repetitively using ultrasound transmitted and received in a plurality of second areas that substantially encompasses the first area to obtain an indication of the quantity of microbubbles in the tissues that are intact over a re-perfusion time, each of the second areas being smaller than the first area, wherein the act of using ultrasound to simultaneously destroy substantially all of the microbubbles in the tissues over a first area comprises using a plane-wave beam of ultrasound to simultaneously destroy substantially all of the microbubbles in the tissues over the first area. Like the prior art techniques referred to in paragraph [008] of the present specification, a plane wave is used to destroy all of the

microbubbles in a broad area of tissue. But instead of using echoes from this destruction for imaging, the method of Claim 11 ignores the returns from the destruction events and instead repetitively transmits and receives ultrasound from smaller areas encompassed within the broader area to acquire echoes from new, intact microbubbles which are highly resolved to obtain an indication of new microbubble re-perfusion. Brock-Fisher et al. are unconcerned with microbubble destruction and measuring re-perfusion, but use smaller apertures to transmit lower energy pulses to differentially distinguish harmonic signal content. The smaller transmit apertures, by definition, transmit beams over broader areas, not smaller areas as the Examiner contends. Thus, it is respectfully submitted that the combination of the prior art technique with Brock-Fisher et al. cannot render Claim 11 and its dependent claims unpatentable.

B. Whether Claim 7 was correctly rejected under 35 U.S.C. §103(a) as being unpatentable over the prior art and Brock-Fisher et al. in view of US Pat. 5,706,819 (Hwang et al.)

Claim 7, which calls for performing the method of Claim 1 while transmitting the imaging ultrasound at a first frequency and receiving echoes at a harmonic of the first frequency, was rejected as being unpatentable over the prior art technique and Brock-Fisher et al., to which Hwang et al. was added. Hwang et al. describes a two-pulse, phase-

modulation technique for separating harmonic echo components, whereas Brock-Fisher et al. describes a two-pulse, amplitude-modulation technique for the same purpose. Hwang et al., like Brock-Fisher et al., is unconcerned with microbubble destruction and imaging the re-perfusion of microbubbles. Like Brock-Fisher et al., Hwang et al. does not show or suggest destroying microbubbles in a broad area with a plane wave, then following the destruction by successively imaging the inflow of microbubbles with a succession of imaging transmit and receive beams directed to smaller areas within the broad area to produce highly resolved images of re-perfusion. Hwang et al. does not suggest aperture variation as Brock-Fisher et al. do, since Hwang et al. are not using power modulation. Since Hwang et al. adds nothing to the combination of the prior art and Brock-Fisher et al. that would render Claim 1 unpatentable, it is respectfully submitted that Claim 7 is patentable over the prior art, Brock-Fisher et al., and Hwang et al. by reason of its dependency from Claim 1.

VIII. CONCLUSION

Based on the law and the facts, it is respectfully submitted that Claims 1, 4, 5, 8, 11 and 12 are patentable over the prior art description in the specification and Brock-Fisher et al., and that Claim 7 is patentable

over the prior art, Brock-Fisher et al., and Hwang et al. Accordingly, it is respectfully requested that this Honorable Board reverse the grounds of rejection of Claims 1, 4, 5, 8, 11 and 12 of this application which were stated in the September 23, 2009 Office action being appealed.

Respectfully submitted,

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APPENDIX A: CLAIMS APPENDIX

The following Claims 1, 4, 5, 7, 8, 11 and 12 are the claims involved in this appeal.

1. (previously presented) A method of obtaining an ultrasound perfusion image of tissues perfused with blood containing microbubbles, the method comprising:

transmitting a plane wave of microbubble-destroying ultrasound into the tissues, the plane wave of microbubble-destroying ultrasound encompassing a first area of the tissues, the microbubble-destroying ultrasound having an intensity that is sufficient to destroy microbubbles in the tissues that are insonified by the microbubble-destroying ultrasound;

repetitively transmitting a plurality of beams of imaging ultrasound into the tissues, each beam of imaging ultrasound having a second area that is smaller than the first area, the imaging ultrasound having an intensity that is substantially insufficient to destroy microbubbles in the tissues that are insonified by the imaging ultrasound;

receiving reflections from each of the transmitted imaging ultrasound beams in respective receive beams, each of the receive beams having a third area that is smaller than the first area; and

processing the received reflections over a sufficient period to allow re-perfusion of the tissues to provide an ultrasound perfusion image.

2. (canceled)

3. (canceled)

4. (previously presented) The method of claim 1 wherein the act of transmitting a plane wave of microbubble-destroying ultrasound into the tissues comprises transmitting a single plane wave of microbubble-destroying ultrasound into the tissues.

5. (previously presented) The method of claim 1 wherein the act of transmitting a plane wave of microbubble-destroying ultrasound into the tissues comprises transmitting a sequence of plane waves of microbubble-destroying ultrasound into the tissues.

6. (canceled)

7. (original) The method of claim 1 wherein the act of repetitively transmitting a plurality of beams of imaging ultrasound into the tissues and receiving reflections from each of the transmitted imaging ultrasound beams comprises transmitting the beams of imaging ultrasound into the tissues at a first frequency and receiving reflections from the transmitted imaging ultrasound beams at a second frequency that is a harmonic of the first frequency.

8. (original) The method of claim 1 wherein the size of each second area insonified by a respective transmitted imaging beams is substantially equal to the size of the respective third area from which reflections from each of the transmitted imaging ultrasound beams are received.

9. (canceled)

10. (canceled)

11. (previously presented) A method of obtaining an ultrasound perfusion image of tissues perfused with blood containing microbubbles, the method comprising:

using ultrasound to simultaneously destroy substantially all of the microbubbles in the tissues over a first area; and

repetitively using ultrasound transmitted and received in a plurality of second areas that substantially encompasses the first area to obtain an indication of the quantity of microbubbles in the tissues that are intact over a re-perfusion time, each of the second areas being smaller than the first area,

wherein the act of using ultrasound to simultaneously destroy substantially all of the microbubbles in the tissues over a first area comprises using a plane-wave beam of ultrasound to simultaneously destroy substantially all of the microbubbles in the tissues over the first area.

12. (original) The method of claim 11 wherein the act of using ultrasound to simultaneously destroy substantially all of the microbubbles in the tissues over a first area comprises using a broad beam of ultrasound to simultaneously destroy substantially all of the microbubbles in the tissues over the first area.

13-19. (canceled)

APPENDIX B: EVIDENCE APPENDIX

None. No extrinsic evidence has been submitted in this case.

APPENDIX C: RELATED PROCEEDINGS APPENDIX

None. There are no related proceedings.